"DESIGN AND DEVELOPMENT OF LIPID-POLYMER HYBRID NANOPARTICLES FOR COMBINATORIAL DRUG DELIVERY"

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By

Mrs Disha Chouhan

M.Pharm.

GUIDE

Dr Rajesh Mujariya

M.Pharm., PhD

INSTITUTE OF PHARMACEUTICAL SCIENCE AND RESEARCH

SARDAR PATEL UNIVERSITY, BALAGHAT (M.P.),

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1. INTRODUCTION

1. Introduction

In recent years, the application of nanotechnology has been translated to medicine. Nanotechnology encompasses the design, synthesis, and characterization of materials and or devices, which are functionally organized in at least one dimension on the nano-scale (Ahirwar CS, 2017).

The use of these nanoscale or nanostructured materials in medicine, termed as Nanomedicine, has unique medical properties and effects owing to the small size (1 –1000 nm) and structure. The ability to engineer and control materials in this size rage results in new medical efforts, innovative chemistry techniques, and novel manufacturing approaches (Ahirwar CS, 2017)

Nanomedicine has the capacity to change the landscape of healthcare and drug delivery by enhancing the develop ability of biologically active drug candidates with poor pharmaceutical properties such as solubility and circulation half-life. Nanomedinces and nanomaterials are engineered to have specific functions, which utilize the physical properties and characteristics or diagnosis and treatment of disease. These materials are able to be used as carriers to cross membranes, mediate molecular interactions, and detect molecular changes. Nanomaterials have a high surface to volume ratio. This increased surface area can be coated or tagged with other molecules, which results in the formation of multifunctional nanomaterials. Nanomaterials can be engineered to have different shapes, sizes, surface chemistry, particle density, and chemical compositions. Because of their design, nanomedicines have applications in drug delivery, in vivo and in vitro diagnostics, biomaterials, active implants, in vivo imaging, biosensing, cell labeling, and tissue engineering. In vivo imaging employs the use of magnetic nanoparticles, quantum dots, fluorophores, and carbon nanotubes. An example is Gastromark (ferumoxsil®), which is a marketed product composed of superparamagnetic iron oxide nanoparticles used as a contrast agent for magnetic resonance imaging. Fluorescent quantum dots are nanocrystals that have higher extinction coefficients than traditional fluorophores, which makes this technology useful for imaging. Carbon nanotubes can act as biocompatible supportive substrates that can incorporate fluorophores and other molecules. Using nanomaterials for in vivo imaging is a faster, less invasive, and a

more accurate way to diagnose diseases and to monitor disease states and progression. In the future, these types of imaging probes may be able to assist surgeons in locating tumors within the body and to identify adjacent structures. In vitro diagnostics is another application for nanomedicine, which uses nanoparticles, nanowires, nanotubes, nanoarrays, and cantilevers. Lateral flow assays are marketed products that utilize colloidal gold to test ovulation, HIV infection, and pregnancy. In this case, an antibody for a specific analyte is conjugated to the nanoparticle surface (Ahirwar CS, 2017).

Gold nanoparticles are widely used because they have good stability, which avoids the chance of false positive readings. With the use of these materials, disease detection can be quick, high throughput, and more accurate by using biomarkers with higher sensitivity. In the future, novel analytes could be measured such as Alzheimer's plaques. Using nanomaterials for in vitro diagnostics is advantageous because they can improve sensitivity, reduce cost, and consume less of the sample. Biomaterials have mechanical properties than can be used as medical implants, dental restoratives, and bone substitutes. One example of a biomaterial is the nanoparticle composite found in the dental restorative Filtek Supreme®, which is a marketed product produced by 3M. Vitoss® is a marketed nanohydroxyapatite based product that is used in the repair of bone defects. Another example of biomaterials in the market is Anticoat®, which is a silver nanoparticle based wound dressing. Nanomedicines have been especially successful as drug delivery vehicles (Ahirwar CS, 2017).

1.1 Techniques for the fabrication of lipid polymer hybrid nanoparticles (LPHNPs) (Badwaik HR, 2019)

The techniques for the preparation of LPHNPs are different from the preparation methods for polymeric nanoparticles and liposomes. Previously, an intricate two step synthesis method was employed for the synthesis of LPHNPs. In this technique, the first step involved the formation of polymeric nanoparticles followed by incorporating it within the liposomes. This complicated process also deteriorates the physicochemical properties of the hybrid nanoparticles. For simplifying the technique, a more facile single step synthesis comprising of a combination of nanoprecipitation and self-assembly method has been reported. (Badwaik HR, 2019)

1.1.1 Anticancer drug delivery

Recently, LPHNPs have proved to be a promising novel approach for the delivery of anticancer therapeutics. These formulations help in the improved biocompatibility and stability, increased circulation time in the bloodstream, and target specific drug delivery. They also possess the capability to deliver a combination of drugs simultaneously in a controlled manner for better efficacy. For example, doxorubicin (DOX) and indocyanine green (ICG) loaded PLGA-lecithin-PEG nanoparticles (DINPs) were prepared by implementing a single-step sonication technique. As compared to the chemo or photothermal treatment alone, the DINPs containing the combination of drugs with laser irradiation synergistically induced the apoptosis and death of DOX-sensitive MCF-7 and DOX resistant MCF-7/ADR cells, and suppressed MCF-7 and MCF- 7/ADR tumor growth in vivo. On the other hand, Wang., et al.synthesized core shell lipid-polymer hybrid nanoparticles (CSLPHNPs) with PLGA core and lipid layer loaded with docetaxel and clinically used inhibitor of sphingosine kinase 1 (SK1) FTY720 (fingolimod). CSLPHNPs could significantly target tumor cells and exhibited reduced side effects in comparison to free drugs, mainly, reversing lymphopenia induced by FTY720. (Badwaik HR, 2019)

1.1.2 Antimicrobial drug delivery

Bacterial biofilms is a community of bacterial cells enclosed by a self-secreted matrix of extracellular polymeric substances (EPS). These bacterial populations can evade the immune system and are highly resistant to the conventional antibiotics. The antibiotic delivery by means of LPHNPs is widely investigated to counter such bacterial biofilms due to their unique physicochemical properties, superb biofilm affinity, and ability to penetrate sputum. These hybrid nanoparticles could significantly deliver the antibiotics to bacterial biofilm, and hence enhances their antibacterial activity. (Badwaik HR, 2019)

1.1.3 Gene delivery

In the recent years, the potential of LPHNPs for gene delivery has been widely investigated by the researchers. Due to the same features of LPHNPs for drug delivery (high stability, extended circulation time, high biocompatibility and ability to get escaped from immune recognition), it has also been employed for gene delivery. (Badwaik HR, 2019).

1.2 Method of preparation

Different methods have been employed for the fabrication of hybrid nano-carriers depending upon their chemical composition and applications. The lipid-polymer hybrid, polymer inorganic hybrid, metal (gold, silver or iron) polymer, silica (SiO2) based hybrid nano-systems and hybrid polymeric nano-carriers have been most widely investigated. Most of these hybrid carriers utilized two distinctive fabrication approaches. First, a two-step conventional approach process, in which the inner core and outer shell are prepared separately and then are co incubated for the formation of hybrid nanoparticle. The second approach is the single step, in which various state-of-the art techniques of the self-assembling are being incorporated. These processes are further modified with different chemical moieties to obtain versatile hybrid nanoparticles meeting specific need of therapy. (Asadullah M, 2017)

1.2.1 Conventional two-step method

It was the first technique employed for the fabrication of hybrid nanocarriers. The inner core and outer shell components are prepared in two separate steps employing suitable polymers and chemicals and are then combined to form the hybrid nanoparticle. The foremost type of core shell hybrid nanoparticles contained a core of the polymeric nanoparticles and an outer shell of preformed lipid component such as liposome or lipoparticles in appropriate ratios. Further, the single or multilayered shell is prepared with other techniques such as sonication, extrusion or high pressure homogenization and vortexing (Asadullah M, 2017)

The polymeric core is prepared by:-

- emulsification-solvent evaporation or solvent diffusion,
- desolvation, nanoprecipitation,
- sonication
- high pressure homogenization

1.2.2. Modified two-step methods

The modifications to the conventional two step method such as spray drying and lithographic molding processes have also been employed for fabrication of hybrid nanoparticles. The inner core is prepared by the spray drying which is dispersed in an appropriate Hybrid Nano-carriers for Potential Drug Delivery solvent containing the lipid, polymer or any inorganic material. The spray dried lipid coated core shell hybrid nanoparticles were collected after the

completion.Freeze or spray dried inhalation hybrid nanoparticles of levofloxacin, ciprofloxacin and isoniazid coated with multiple layers of the lipids were prepared using double emulsion solvent evaporation technique. These hybrid nanoparticles showed better inhalation efficiency, emitted particle size and diameter compared to the conventional two step methods. Another investigations employed nanospray drying for fabrication of hybrid nanoparticles using polyglutamic acid, poly lysine nanoparticles coated with the lipid materials. Recently, Keloglu et al. employed jet spray drying technique for the fabrication of hybrid microfibers-nanoparticles having low density and greater strength using PLGA and poly lactic acid (PLA). A soft lithography particle molding technique was also utilized for the preparation of hybrid nanocarriers for the delivery of genes to various diseases. De Simon and his coworkers prepared the nanosized particles using the particle replication approach on the silicon wafers. The technique was referred to as Particle Replication in Nonwetting Templates (PRINT). The process involve the dissolution of the polymer (e.g., PLGA, PLA) in an organic solvents such as dimethyl formamide, methyl acetate and/or dimethyl sulfoxide along with the material to be encapsulated. The PRINT molding device was employed to fabricate the nanoparticles which later were harvested with the help of polyethylene terephthalate sheet. It produces the particles of different shapes and a wide size range depending upon the size of the molding cavities. (Asadullah M, 2017)

1.2.3. Single-step preparation methods

The low encapsulation efficiency due to the leakage of the drugs from the inner core during second step, batch variability and large time consumption are the common problems associated with the conventional two step methods. These constraints can be overcome by designing the simple method that utilized the single step approach and also provide better control on the content uniformity, reproducibility and other characteristics of the system. The method involves the mixing of two different solutions containing the polymer and lipid that self-assembled to form the particles with the core shell hybrid structure. The polymer is dissolved in an appropriate organic solvent while the lipid solution is prepared in the water that may utilize the small fraction of organic solvent as solubilizing agent. The solution containing polymer is added to the lipid phase where the polymer precipitate to formed the nanoparticles and the lipid is self-assembled at the surface to form the hybrid nanoparticles. Single-step preparation is usually achieved by nanoprecipitation, emulsification-solvent evaporation and solvent diffusion methods. (Asadullah M, 2017)

1.2.3.1. Emulsification solvent evaporation method

Emulsification solvent evaporation method is the most commonly employed single step approach for the fabrication of hybrid nanocarriers. The single emulsification solvent evaporation and double emulsification solvent evaporation (DESE) techniques are employed depending upon the nature and solubility of encapsulating drug. In the ESE method, the oil phase is formed by dissolving the polymer and the drug in the water immiscible organic solvent. The aqueous solution containing the lipid portion which act as a stabilizer itself during the self assembling process. The organic phase is then added dropwise into the aqueous phase under the sonication or stirring at the constant speed that results in the formation oil in water emulsion. During the emulsification process, the hydrophobic part of the lipid is adsorbed on the inner core material while the hydrophilic parts arrange themselves toward the aqueous medium forming the lipid coated hybrid nanoparticles. (Asadullah M, 2017)

1.2.3.2. Nanoprecipitation

This method is also known as salting out method. It is a well known method for fabrication of hybrid nanoparticles of size less than 100 nm. This method employs two miscible solvents with different solubilizing capacity for the polymer. First, the polymer core is formed by solubilizing in solvent of greater solubility designated as good solvent which is then added to less soluble solvent designated as poor solvent. The two solutions are mixed by dropwise addition, stirring or sonication. Good solvent being miscible with poor solvent diffuses into later, leaving behind the core nanoparticles due to the precipitation of the polymer. The core forming polymer and lipophilic drug are solubilized in a water-miscible organic solvent like acetone, acetonitrile or ethanol. The lipids, inorganic salts or silica are dispersed in water with moderate heating (~60–75°C) and/or addition of hydroalcoholic mixtures for proper dispersion of the lipids. The hydrophilic drugs are added to the aqueous phase containing dispersed lipids. The polymer containing organic phase is then added dropwise to lipid dispersion with continuous stirring to precipitate the polymer into nanoparticles. The monodispersed hybrid nanoparticles are collected after suitable application of vortexing, homogenization or ultrasonication. Concurrent to the precipitation process, the self-assembly of lipid molecules around the polymer molecules occurs due to the hydrophobic interactions. The polymer core captures the hydrophobic tails of lipid while the heads are facing toward

the aqueous phase. Continuous stirring of dispersion for several hours is helpful in uniform lipid coating of hybrid nanoparticles and to ensure the complete removal of organic solvent. Rotary evaporator may also be helpful for the removal of organic solvents. The literature suggests 10% ethanolic solution is employed for solubilization of lipids and PEG may enhance the stability of hybrid nanoparticles. (Asadullah M, 2017)

1.2.3.3. Sonication

Sonication is a fast technique for the fabrication of hybrid nanoparticles which utilizes ultrasonic waves rather than vortexing, solvent evaporation or heating. In this method, the two solutions designated as organic and aqueous phases lead to formation of inner core (polymer) and outer shell or coating materials (lipids), respectively. The sonication has been employed by Fang et al. for the fabrication of hybrid nanoparticles of lecithin-PEG and PLGA by using this approach. The PLGA was dissolved in acetonitrile while the lecithin and the PEG were added in 4% ethanol solution. The former solution was carefully pipetted into the hydroalcoholic solution (aqueous to organic ratio was kept as 10:1). The hybrid nanoparticles were produced as this 'cocktail' mixture was placed in sonicator bath for five minutes at a frequency of 42 kHz and a power of 100 W. The main advantage of this technique is the formation of stable hybrid nanoparticles with short processing time and production rate is 20 times than other processes. (Asadullah M, 2017)

1.2.3.4. Green technology for the preparation of hybrid nanocarriers

The use of green technology has revolutionized the synthesis of hybrid nanocarriers due to the ecofriendly procedures that mitigate the threats of toxic impurities and use of the organic solvents. These ecofriendly approaches also provided low operating cost, better stability, compatibility and minimum health hazards. The literature has suggested the successful implementation of solvent free approaches to formulate nanosized systems for the targeted delivery of different therapeutic and diagnostic moieties. The heat chill method has been employed to prepare micelles using the amphiphilic diblock and triblock copolymers of polycaprolactone (PCL) for the encapsulation of insulin without using any organic solvent and has provide better stability of the entrapped proteins which are liable to denaturation in the presence of different organic solvents. (Asadullah M, 2017)

1.2.3.5. Preparation of organic/inorganic hybrid nanoparticles

The concept of combining the characteristics of organic and inorganic components is quite old since the time of Egyptian inks. However, the modern organic-inorganic hybrid systems are not prepared by simple mixing these materials but may involve the weak electrostatic linkages (H-bonding or van der Waals forces) or strong chemical bonds, i.e., covalent bonds. Multiple strategies are employed for the preparation of these hybrid particles. (Asadullah M, 2017)

These include ;-

- polymerization of the different monomers, organosilanes and the metal oxides,
- selfassembly of different structural components at nanoblock level with different organic and metal components,
- the functionalization of preformed nanocarriers with different organic compounds and
- making the core with organic materials and coating with the silica and different metallic components

1.3 Characterization

After successful synthesis of various lipid coated hybrid nanoparticles, the particles were characterized using different state-of-art analytical technique including :-

- Dynamic Light Scattering (DLS),
- Scanning Electron Microscope (SEM), and
- Transmission Electron Microscopy (TEM).

1.3.1 Particle Size and Polydispersity Index (PDI)

Particle size measurements were performed by using dynamic light scattering (DLS) technique (Malvern Zetasizer, ZEN 3600). Three subruns were carried out per measurement, and the average values were taken. (Ahirwar CS, 2017).

1.3.2 Zeta Potential Zeta potential

Measurements were taken using the Malvern Zetasizer (ZEN 3600) in which the electrophoretic mobility on the surface of the nanostructures was measured. The measurements were carried out at room temperature with the backscatter angle of 173°. Three

subruns were carried out per measurement and the average values were taken. (Ahirwar CS, 2017).

1.3.3 Scanning Electr on Micr oscopic (SEM)

Analysis Scanning electron microscopy is the technique used to look at morphology and surface structure of the materials. Samples for SEM were prepared by dropping 5 μL of a nanoparticle solution onto a polished silicon wafer. After drying the droplet at room temperature overnight, the sample was coated with chromium and then imaged under Phillips XL 30 ESEM. (Ahirwar CS, 2017).

1.3.4 Transmission Electron Microscopic (TEM) Analysis

Transmission electron microscopy is the technique used to look at the internal structure of the materials. In order to understand the internal structure of hybrid nanoparticles, a drop of the nanoparticle solution at a concentration of 4 μg/mL was deposited onto a glow discharged carbon-coated grid. Five minutes after the sample was deposited the grid was rinsed with ten drops of distilled water. A drop of 1% uranyl acetate stain was added to the grid. The grid was subsequently dried and visualized using a FEI 200KV Sphera microscope. (Ahirwar CS, 2017).

2. LITERATURE REVIEW

2.1 Tahir N *et al* (2019) was studied the useful insight about the lipid-polymer hybrid nanoparticles (LPHNPs) that can be prepared by using the different structural components including the synthetic and natural polymers and lipids. Among these, we also explain the various methods to prepare the LPHNPs with various desired characteristics. Finally, the various therapeutic and clinical applications have been presented briefly.

2.2 Badwaik HR *et al* (2019) was studied Recent advances in the field of nanomedicine have promoted the development of several novel nanoformulations. Among them, the lipid polymer hybrid nanoparticles (LPHNPs) have gained an increasing attention by the researchers in this field owing to the attractive properties such as high stability and biocompatibility, prolonged circulation time, high drug loading capacity, stealth characteristics, controlled drug release properties, and superior in vivo efficacy. They possess the advantages of both the liposomes and polymeric nanoparticles which makes them a chosen one in the field of drug and gene delivery. The application of LPHNPs has not only been restricted to single drug delivery, but has been expanded to combinatorial and targeted therapeutics, and also for the effective delivery of genes, vaccines and diagnostic agents. This review highlights the recent advancements of LPHNPs in the field of drug delivery, including the types of hybrid nanoparticles, fabrication techniques, and their applications for single and combinatorial drug delivery, and gene therapeutics.

2.3 Ahirwar CS *et al* (2017) was studied the Use of polymeric nanoparticles and lipid carrier systems, including liposomes, solid lipid nanoparticles and nanostructured lipid carriers which has limitations such as drug leakage and high water content of dispersions. Thus, lipid polymer hybrid nanoparticles have been explored by the researchers to provide a better effect using biomimetic characteristics of lipids and architectural advantage of polymeric core and finally producing a system which overcomes the limitations of both polymeric nanoparticles and lipid carrier systems.

2.4 Asadullah M *et al* (2017) was studied and produce a chapter in book stating that Nanocarriers provided the versatile platform for the delivery of various therapeutic and diagnostic agents. Liposome, niosomes, polymeric and solid lipid nanoparticles are the most promising nanocarriers that have been entered in the clinical trials and become commercially available. However, each system has been associated with some problems that can be minimized by using the combinatorial approach of hybrid nanocarriers. These hybrid systems combine the benefits of different structural components to synergize the outcome of the therapy. In this chapter, the different types of hybrid nanocarriers have been described with particular emphasis on the brief rationale for the development of these hybrid nanocarriers along with different fabrication approaches with greater emphasize on the lipid polymer hybrid nanoparticles. A brief description factors governing the optimized response characteristics and their potential application of these hybrid nanoparticles are also presented.

2.5 Dave V *et al* (2017) was studied the Poly lactic acid is a biodegradable, biocompatible, and non-toxic polymer, widely used in many pharmaceutical preparations such as controlled release formulations, parenteral preparations, surgical treatment applications, and tissue engineering. In this study, we prepared lipid-polymer hybrid nanoparticles for topical and site targeting delivery of Norfloxacin by emulsification solvent evaporation method (ESE). The design of experiment (DOE) was done by using software to optimize the result, and then a surface plot was generated to compare with the practical results. The surface morphology, particle size, zeta potential and composition of the lipid-polymer hybrid nanoparticles were characterized by SEM, TEM, AFM, and FTIR. The thermal behavior of the lipid-polymer hybrid nanoparticles was characterized by DSC and TGA. The prepared lipid-polymer hybrid nanoparticles of Norfloxacin exhibited an average particle size from 178.6 ± 3.7 nm to 220.8 ± 2.3 nm, and showed very narrow distribution with polydispersity index ranging from 0.206 ± 0.36 to 0.383 ± 0.66. The surface charge on the lipid-polymer hybrid nanoparticles were confirmed by zeta potential, showed the value from þ23.4 ± 1.5 mV to þ41.5 ± 3.4 mV. An Antimicrobial study was done against Staphylococcus aureus and Pseudomonas aeruginosa, and the lipid-polymer hybrid nanoparticles showed potential activity against these two. Lipid-polymer

hybrid nanoparticles of Norfloxacin showed the %cumulative drug release of 89.72% in 24 h. A stability study of the optimized formulation showed the suitable condition for the storage of lipid-polymer hybrid nanoparticles was at 4 ± 2 _C/60 ± 5% RH. These results illustrated high potential of lipid-polymer hybrid nanoparticles Norfloxacin for usage as a topical antibiotic drug carriers.

2.6 Jinjun S *et al* (2014) was studied the development of controlled-release nanoparticle (NP) technologies has great potential to further improve the therapeutic efficacy of RNA interference (RNAi), by prolonging the release of small interfering RNA (siRNA) for sustained, long-term gene silencing. Herein, author present an NP platform with sustained siRNA-release properties, which can be self-assembled using biodegradable and biocompatible polymers and lipids. The hybrid lipid–polymer NPs showed excellent silencing efficacy and the temporal release of siRNA from the NPs continued for over one month. When tested on luciferase-expressed HeLa cells and A549 lung carcinoma cells after short-term transfection, the siRNA NPs showed greater sustained silencing activity than lipofectamine 2000-siRNA complexes. More importantly, the NP-mediated sustained silencing of prohibitin 1 (PHB1) generates more effective tumor cell growth inhibition in vitro and in vivo than the lipofectamine complexes.

3. AIM AND OBJECTIVE

3.1 Aim

To Design and Development of Lipid-Polymer Hybrid Nanoparticles for Combinatorial Drug Delivery

3.2 Objective

1. To formulate a drug delivery vehicle that has versatile functionality.
2. To formulate a good serum stability.
3. To formulate a vesicle which is circulates in the body long enough to reach the targeting tissues.
4. To Formulate biocompatible a drug delivery vehicle.
5. To Formulate a Controlled drug releases kinetics.
6. To Enhance Pharmacokinetics.

4. PLAN OF WORK

4.1. Literature survey

4.2. Procurement of Drugs and Excipients

4.3. Preformulation study

4.4. Synthesis of Hybrid Nanoparticles

4.5 Characterization of Hybrid Nanoparticles

- a) Particle Size and Polydispersity Index (PDI)
- b) Zeta Potential
- c) Scanning Electron Microscopic (SEM) Analysis
- d) Transmission Electron Microscopic (TEM) Analysis

4.5. Formulation of Combinatorial Drug Delivery with Lipid-Polymer Hybrid Nanoparticles

4.6. Evaluation of Formulations

- a) Drug Loading
- b) UV-Vis Spectroscopy
- c) Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES)
- d) Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC)
- e) In Vitro Drug Release
- f) In Vitro Cytotoxicity

4.7 Results and Discussion

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(Mrs Disha Chouhan)
M.Pharm.
Research Scholar

(Dr Rajesh Mujariya)
M.Pharm., PhD
Research Guide